Remarks

Prosecution has been reopened in response to the Appeal Brief filed on December 7, 2009. The Office Action mailed on May 19, 2009 was vacated and was replaced with the Office Action mailed March 16, 2010. The rejections alleged constitute the complete set of rejections applied to the application.

Claims 20 and 24–40 are currently pending, with claim 20 being the sole independent claim. Claims 1–19 and 21–31 were canceled previously. Claims 20, 24, 25, 31, 32, and 34 are amended. Claim 20 is amended to remove the terms "about" with respect to the recited ratio of acid-insoluble polymer to film-forming, water soluble polymer. Claims 24 and 25 are amended to correct the spelling of the term "proteinaceous." Support for this amendment is found on p. 3, line 30 of the originally filed specification (where it is also misspelled and has been corrected herein). Claim 30 is amended to correct the spelling of the term "polyethylene." Support for this amendment is found on p. 4, line 7 of the originally filed application (where it is also misspelled and has been corrected herein). Claims 31, 32, and 34 are amended to change the term "solution" to "solvent" to provide correct antecedent basis. Support for this amendment is found in claim 20.

Rejection Under 35 U.S.C. § 112, Second Paragraph is Rendered Moot

The Examiner rejected claims 31, 32, and 34 under 35 U.S.C. § 112, second paragraph, as allegedly having insufficient antecedent basis in depending from claim 20. Claims 31, 32, and 34 are amended to change the term "solution" to "solvent." Accordingly, the Examiner's asserted basis for the rejection is now moot, and Applicants respectively request that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 103 Are Traversed

Venkateswara, in view of the Ullah patent, and Matthews

The Examiner alleged that claims 20, 24–25, and 27–40 are unpatentable over WO 01/24780 (Venkateswara), in view of U.S. 6,331,316 (the Ullah patent) and U.S. 4,816,259 (Matthews). Office Action at page 4. In view of the following remarks, the rejection is respectfully traversed.

The following criteria must be met in order to establish a proper *prima facie* case of obviousness: (1) the prior art reference (or references, when combined) must teach or suggest **all the claim limitations**; *see In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); (2) the combination of references must teach the **predictable use** of prior art elements according to their established functions; *see KSR*, 550 U.S. at 417; and (3) there must be a **reasonable expectation of success** in combining the teachings of the references. Further, in *KSR*, the Supreme Court stated that the analysis supporting a rejection under 35 U.S.C. § 103(a) should be made *explicit*, and that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art references]" in the manner claimed. See *KSR*, 550 U.S. at 418, *citing In Re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds ***cannot be sustained by mere conclusory statements***, instead, there must be some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness. . . " (emphasis added)). The Court in *KSR* also expressly stated that it is legally insufficient to conclude that a claim is obvious just because a feature of a claim can be independently shown in the art.

> A patent composed of several elements is ***not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art***.

KSR, 550 U.S. at 418 (emphasis added). When determining the differences between alleged prior art references and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 U.S.P.Q. 871 (Fed. Cir. 1983). *See* MPEP § 2141.02(I).

The claimed invention is an enteric soft capsule formed from a gel mass composition comprising a film-forming, water-soluble polymer, an acid-insoluble polymer, and an alkaline aqueous solvent; wherein the ratio of acid-insoluble polymer to film-forming, water soluble polymer is from 30:70 to 45:55 by weight; the final pH of the gel mass is less than or equal to 9 pH units; and the moisture content of the enteric soft capsule shell formed from the gel mass composition is from 2% to 10%. The dependent claims further recite particular parameters of the gel mass. The invention provides a direct method for manufacturing enteric soft capsules without the need for coating the capsule with an enteric composition. Furthermore, the soft capsule does not require cross-linking to gain its enteric character. Fill materials can be hydrophobic, hydrophilic, liquid, solid, or combinations thereof.

The Examiner alleges that Venkateswara discloses an enteric soft capsule shell formed from a gel mass composition comprising a film-forming, water-soluble polymer, including gelatin, an acid insoluble polymer, including hydroxypropyl methylcellulose phthalate, and an alkaline aqueous solvent and that the acid-insoluble polymer can be 40% by weight of the dried shell. The Examiner admits that Venkateswara is silent on the pH and water content of the composition.

Specifically, the Examiner asserted that:

> Venkateswara et al. discloses the acid-insoluble polymer can be 40% by weight of the dried shell (pg. 5, lines 25–27). Given this disclosed weight percent of acid-insoluble polymer therefore, it can be concluded that the remaining polymer is present at a ratio of 30:70 (42%).

Office Action at page 4. The cited lines of Venkateswara, describe "a preferred embodiment" as follows: "The amount of such enteric polymer employed may range from 5.0–40.0 percent, preferably 5.0–25.0 percent by weight with reference to the dried shell." Venkateswara, p. 5, lines 25–27. However, contrary to the Examiner's assertion, this passage of Venkateswara does not teach or suggest a ratio of acid-insoluble polymer to film-forming polymer as recited in Applicant's claims.

The Examiner's reasoning appears to presume that ***every component*** of the dried shell other than "enteric polymer" in a composition exhibiting the upper end of the recited range would be a "film-forming polymer" such as gelatin. Based on this assumption, the Examiner asserts that, "it can be concluded that the remaining polymer is present at a ratio of 30:70 (42%)". This assertion is wholly unsupported in the reference, for at least the reason that the cited passage provides no information on the other components or total composition of the dried shell.

Applicants have taken the raw mass values disclosed by Venkateswara and converted them to ratios for the sole purpose of rebutting the Examiner's arguments. A review of the exemplified compositions demonstrates that no ratio of enteric polymer to gelatin exceeds 10:30 (whole number: 0.333), compared to 30:70 (whole number: 0.43), which is the lowest end of the ratio range claimed by the Applicants. These values are substantially lower than those assumed by the Examiner based on the upper end of the recited percentage of enteric polymer in a dried shell quoted in Venkateswara. The Examples provided in Venkateswara, when converted by Applicants to whole number ratios of enteric polymer to film-forming polymer, are completely outside the range claimed by the Applicants. *See* Venkateswara, pp. 8–17. Venkateswara discloses compositions, which when converted to whole number values of enteric polymer to film-forming polymer, range from 0.188 (7.5:40) to 0.333 (10:30). In contrast,

Applicants' claimed ranges are from 0.43 (30:70) to 0.82 (45:55), and thus are outside the ranges found in Venkateswara. Consequently, Venkateswara fails to teach or suggest ***any*** percentage or amount of enteric polymer in a defined ratio with the film-forming polymer. As noted, ***no ratio whatsoever*** is taught in the passage of Venkateswara quoted in the Office Action.

The Examiner has misinterpreted the disclosure of Venkateswara and alleged that it implicitly discloses a ratio of enteric polymer to water soluble polymer. The secondary references, the Ullah patent and Matthews, are not cited for any teaching or suggestion that cures the deficiencies of Venkateswara. Accordingly, the Ullah patent and Matthews fail to cure the deficiencies of Venkateswara. No *prima facie* case of obviousness has been established because no combination of the references provides all elements of the invention as claimed.

Even assuming, solely for the sake of argument, that the Examiner has established a *prima facie* case of obviousness, the rejection should be withdrawn for at least the following reasons. Of course, Applicants do not intend to imply in any way that the Examiner has established a *prima facie* case of obviousness by asserting the following arguments.

Applicants' claimed ratio of enteric polymer to film-forming polymer was shown by Applicants to be the lowest level of enteric polymer to achieve acceptable results and that lower ratios produced "border quality" compositions. *See* Application, page 15, lines 22–29. Thus, the ranges taught by Venkateswara would not produce acceptable stability in the Applicants' formulation. Consequently, Applicants have disclosed and claimed a critical lower limit of a range of the ratio of enteric polymer to film-forming polymer in the composition as claimed. Accordingly, even assuming solely for the sake of argument that a *prima facie* obviousness was established, this evidence of unpredictable results (advantageous properties empirically determined by the inventors) rebut the *prima facie* assertion.

In the present case, Applicants have claimed an enteric formulation with a ratio of acid-insoluble polymer to film-forming polymer of 30:70 to about 45:55 by weight, where the final pH of the gel mass is less than or equal to about pH 9.0 and with a moisture content from about 2–10%. These conditions for forming enteric soft capsules are not taught nor suggested by Venkateswara or the secondary references. Further, all of the elements of the claimed composition are interdependent and must be considered as a whole and not as independent variables.

An additional flaw in the Examiner's reasoning is that combining the independent cited references is apparently presumed to yield predictable results. The Examiner alleges:

> It would have been prima facie obvious to one of ordinary skill in the art to increase the pH of the enteric soft capsule taught by Venkateswara et al. One would have been motivated to do so because Ullah et al. teaches that an increased pH provides a more stable composition for acid labile drugs which may be present [in – *sic*] the core.

Office Action at page 4. In another section, the Examiner alleges one would be "motivated to optimize the pH of the solution in order to maintain the active pharmaceutical ingredients in their desired salt form without any degradation of the active ingredients that may occur due to a change in pH." Office Action at page 5. Further, the Ullah references disclose **enteric coatings** for tablets and beadlets, not enteric soft capsules. The success of this alleged combination is not predictable, even if optimization is undertaken. Furthermore, the asserted motivations for modifying the pH are wholly unsupported. The claimed invention does not recite any features of acid-labile drugs in the core of the capsule. The claimed invention does not recite any features of the salt forms of active ingredients. The claimed feature is that the pH of the gel mass is less than or equal to pH 9.0. *See* Claim 20. Consequently, combining Venkateswara with the Ullah patent would not predictably lead to the claimed invention and the asserted motivations for combining the references are not supported by the facts. Any mention by Ullah of adjustments related to acid-labile drugs in the core of compositions discussed therein cannot rightly be presented as motivation to combine such teaching with any asserted teachings of Venkateswara which does not address this issue or problem. And, in any event, the discussion in Ullah expressly relates to drugs "in the core." This difference runs counter to any assertion of motivation for the combination.

A similar argument is applicable with respect to Matthews. The Examiner alleges that "one would have been motivated to modify the moisture content to be between 8–10% [allegedly taught by Matthews] in order to ensure the integrity of the enteric soft capsules given that enteric soft capsules are known to crack or undergo substantial deformation during manufacturing . . . ." Office Action, at pages 4–5. As above, the Examiner has asserted that combining the alleged teaching of Matthews with Venkateswara will predictably lead to the claimed invention. The assertion that combining independent claim elements to yield predicted properties (as allegedly taught by references) by the "optimization of parameters" is unsupported. This is particularly true with an interdependent chemical composition such as the claimed gel mass, where the variation of one component can change the entire composition and its properties

Matthews discusses an **enteric coating** for gelatin capsules (i.e., the capsule is made first, and then coated with an enteric composition). The disclosed invention is an enteric soft

capsule, not **an enterically coated** soft capsule. The properties disclosed by Matthews are different for at least the reason that the coating must adhere to the surface of the gelatin capsule. In the claimed invention, the soft capsule shell has enteric properties without requiring a coating. The alleged teaching of Matthews regarding moisture content appears to apply to normal soft gelatin capsules that are intended to be coated by an enteric coating. Accordingly, the asserted motivation for modifying the moisture content (i.e., "in order to ensure the integrity of the enteric soft capsules given that enteric soft capsules are known to crack or undergo substantial deformation during manufacturing . . . .") is irrelevant, because the claimed enteric soft capsule shells do not require further processing to become "enteric"— e.g., coating with an enteric composition.

Consequently, neither Venkateswara, the Ullah patent, nor Matthews, either independently or when combined, teaches or suggests the claimed invention. Claim 20 is the sole independent claim. Claims 24–25 and 27–40 depend from claim 20. Thus, claims 24–25 and 27–40 are nonobvious for the reasons that claim 20 is not obvious over Venkateswara, in view of the Ullah patent, and Matthews. If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. Accordingly, the rejection is in error and must be withdrawn.

Venkateswara, in view of the Ullah patent, and Matthews, further in view of Shank

The Examiner alleged that claim 34 is unpatentable over Venkateswara, in view of the Ullah patent and Matthews, further in view of U.S. Patent No. 4,500,453 (Shank). Office Action at page 5. Although the Examiner has stated that "claim 34" is the subject of the rejection, the actual rejection appears to indicate that claim 26, reciting "about 100 to about 250 blooms" was intended. The following remarks traversing the rejection are based on this assumption.

Claim 25 recites that the "proteinaceous film-forming, water soluble polymer" of claim 20 is gelatin. Claim 26 recites that the gelatin of claim 25 is "extracted from animal bones or skin, and has about 100 to about 250 blooms."

The deficiencies of Venkateswara, Ullah patent, and Matthews are as discussed above. Shank is cited as a further secondary reference with Venkateswara, in view of both Ullah references and Matthews. The Examiner alleges that Shank teaches that gelatin obtained from animal bones contains lower molecular weight fractions and that enteric capsule made with gelatin have about 100 to about 250 blooms. No teaching by Shank of any polymer ratios or pH is asserted.

Based at least on the remarks above regarding the deficiencies of Venkateswara, the Ullah patent, and Matthews, it is Applicants' position that the asserted teachings of Shank do not cure the noted deficiencies of the other references. Accordingly, the rejection is in error and must be withdrawn.

Venkateswara, in view of the Ullah publication, and Matthews

The Examiner alleged that claims 20, 24–25, and 27–40 are unpatentable over Venkateswara, in view of US 2001/0051188 A1 (the Ullah publication) and Matthews. Office Action at page 6. In view of the following remarks, the rejection is respectfully traversed.

This rejection does not appear to differ significantly from the similar rejection over the same references and based on the Ullah patent corresponding to a parent of the cited publication. It appears that the "Ullah publication" relates to US Appln No. 09/866,501, which appears to be a continuation-in-part of US Appln No. 09/549,455, which issued as US Pat. No. 6,331,316. There would not appear to be significant differences (tablets discussed in the Ullah patent as compared to beadlets discussed in the Ullah publication) in relation to the Examiner's assertions. Accordingly, it is not clear why the Examiner has generated a multiplicity of rejections based on essentially the same cited disclosure applied against the same claims of the present application. In any event, the rejection is properly traversed, at least in view of the foregoing and the following remarks.

The Ullah publication is cited in an attempt to remedy the deficiencies of Venkateswara for the alleged teaching that the pH of an enteric coating polymer is raised using an alkalizing agent; the pH is raised to a point below the pH wherein the enteric integrity of the polymer could be lost; and this partial acid neutralization provides a more stable composition for the acid labile drug in the core.

The Ullah publication discusses a high drug load **spheronized beadlet** containing an acid labile drug and an **enteric coating** for such beadlet. *See* Ullah publication, *Abstract*. The Examiner alleges that the Ullah publication teaches that the pH of an enteric coating polymer is raised using an alkalizing agent like sodium hydroxide and the pH is raised to a point below the pH wherein the enteric integrity of the polymer could be lost. Allegedly, this partial acid neutralization provides a more stable composition for the acid labile drug in the core. In this regard, Applicants refer to their remarks presented above in relation to the citation of the Ullah patent and the failure of the Ullah patent and the Ullah publication to cure the deficiencies of Venkateswara.

Applicants' remarks regarding the rejection over Venkateswara, in view of the Ullah patent and Matthews, provided above, traverse the asserted basis for this rejection. Accordingly, the rejection is in error and must be withdrawn.

Venkateswara, in view of the Ullah publication, and Matthews, further in view of Shank

The Examiner alleged that claim 34 [again, believed to be a typographical error – claim 26 believed intended] is unpatentable over Venkateswara, in view of the Ullah patent and Matthews, further in view of U.S. Patent No. 4,500,453 (Shank). Office Action at page 8.

This rejection is traversed in view of the substantially similar rejection above, based on the same references except, there, the Ullah patent is cited and, here, the published Ullah application is cited. Accordingly, the rejection is in error and must be withdrawn.

Okajima*, in view of the Ullah publication, and Matthews*

The Examiner alleged that claims 20, 24–25, and 27–40 are unpatentable over U.S. Patent No. 4,138,013 (Okajima), in view of the Ullah publication and Matthews. Office Action at page 8. In view of the following remarks, the rejection is respectfully traversed.

Initially, it is important to note that the Examiner has cut and pasted the same assertions of obviousness for the Okajima reference (*see* page 9, last ¶ and page 12, second ¶ of the Office Action) as that for the Venkateswara reference (*see* page 4, last ¶ of the Office Action) *without changing the name of the reference*. This is indicative of the unsubstantiated and conclusory allegations of obviousness and the lack of the required explicit analysis in support of any *prima facie* assertion. In any event, as illustrated below, Okajima does not teach or suggest the asserted element of Applicants' claimed invention.

The Examiner alleges that the Okajima reference teaches a gel mass composition comprising a film-forming, water-soluble polymer, an acid-insoluble polymer, an alkaline aqueous solvent, and optionally a plasticizer and a coloring agent. It is further alleged that the reference teaches a ratio of acid-insoluble polymer to film-forming polymer being 50:50. The Examiner acknowledges that Okajima does not disclose that the final pH of the gel mass is less than or equal to about 9 pH units and the moisture content of the gel mass is from about 2% to about 10%.

Similar to Venkateswara, the Examiner alleges that Okajima teaches a ratio of acid-insoluble polymer to film-forming polymer. "Okajima et al. illustrates in Example 2 the ratio of acid-insoluble polymer to film-forming polymer being 50:50." Office Action at page 9. The relevant sentence of Example 2 is, "Cellulose acetate phthalate (CAP, 50 g.) is dissolved in 220

ml. of 1.5% aqueous ammonium hydroxide and 50 g. of hydroxypropyl methylcellulose is added thereto."

In Example 2, comparing the amount of CAP (50 g) to the amount of hydroxypropyl methylcellulose (HPMC - 50 g), the apparent "ratio" is a whole number of 1. The single apparent ratio is significantly higher than the maximum recited in Applicants' claimed range. Accordingly, Okajima does not teach or suggest any ratio within Applicants' recited range. None of the cited secondary references are alleged to cure this deficiency.

Okajima fails to teach or suggest the claimed composition and none of the secondary references, alone or in combination, cure the deficiencies of Okajima. For at least this reason, no *prima facie* case of obviousness has been presented. Accordingly, the rejection is in error and must be withdrawn.

Okajima, in view of the Ullah publication, and Matthews, further in view of Shank

The Examiner alleged that claim 34 [again, believed to be a typographical error – claim 26 believed intended] is unpatentable over Okajima, in view of the Ullah publication and Matthews, further in view of U.S. Patent No. 4,500,453 (Shank). Office Action at page 10.

This rejection is traversed in view of the substantially similar rejection above, based on the same secondary references and Venkateswara. Accordingly, the rejection is in error and must be withdrawn.

Okajima, in view of the Ullah patent, and Matthews

The Examiner alleged that claims 20, 24–25, and 27–40 are unpatentable over Okajima, in view of the Ullah patent and Matthews. Office Action at page 11. In view of the following remarks, the rejection is respectfully traversed.

As above, with respect to the parallel rejection based on Venkateswara, this rejection does not appear to differ significantly from the similar rejection over the same references and based on the Ullah publications corresponding to a continuation-in-part application of the cited patent. There would not appear to be significant differences (beadlets discussed in the Ullah publication as compared to tablets discussed in the Ullah patent) in relation to the Examiner's assertions. Again, it is not clear why the Examiner has generated a multiplicity of rejections based on essentially the same cited disclosure applied against the same claims of the present application. In any event, the rejection is properly traversed, at least in view of the foregoing and the following remarks.

The Examiner's arguments based on alleged teachings of the Ullah patent, page 11 of the Office Action are identical to those asserted on page 4 of the Office Action in the rejection based on Venkateswara as primary reference. The asserted teachings of Matthew are also identical to those asserted in the rejection discussed above. Because of the similarities in the asserted teachings of Venkateswara and Okajima, no combination of the cited reference could provide Applicants' claimed invention. For at least this reason, stated in more detail above, no *prima facie* case of obviousness has been established.

Applicants' remarks regarding the rejection over Venkateswara, in view of the Ullah patent and Matthews, provided above, fully traverse the asserted basis for this rejection substituting Okajima for Venkateswara. Accordingly, the rejection is in error and must be withdrawn.

Okajima, in view of the Ullah patent, and Matthews, further in view of Shank

The Examiner alleged that claim 34 [again, believed to be a typographical error – claim 26 believed intended] is unpatentable over Okajima, in view of the Ullah patent and Matthews, further in view of U.S. Patent No. 4,500,453 (Shank). Office Action at page 11.

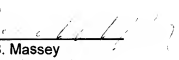
This rejection is traversed in view of remarks above relating to the substantially similar rejection, based on the same references except citing the Ullah publication instead of the Ullah patent. Accordingly, the rejection is in error and must be withdrawn.

Conclusion

Entry of the foregoing amendment is respectfully requested. All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned attorney at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,



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